III. Remarks

Claim 16 has been amended. Support for the amendment can be found on page 4, lines 10–12 of the specification.

A. Claim Rejections Under 35 U.S.C. §103(a)

Claims 16–21, 28 and 31–32 stand finally rejected under 36 U.S.C. 103(a) as being unpatentable over PCT/1B97/01 634 to Rudin et al. ("Rudin et al."), in view of United States Patent No. 4,853,225 to Wahlig at al. ("Wahlig et al."), and further in view of Flautre et al. ("Flautre et al.") Journal of Materials Science: Materials In Medicine, Evaluation of Hydroxyapatite Powder Coated with Collagen as an Injectable bone Substitute: Microscopic Study in Rabbit, 7, pp. 63–67 (1996).

In making the rejection over the combined teachings of Rudin et al. and Walig et al., the Examiner admitted that Rudin et al. does not teach the incorporation of a protein, protein hydrolyzate, or protein hydrolyzate derivative into a composite of these materials and hydroxyapatite. However, the Examiner cited Wahlig et al. for teaching a hydroxyapatite composition which comprises collagen or from 1–20% of a collagen degradation product (*see* col 4 lines 62–67) which includes gelatin.

Wahlig et al. teaches an implantable medicament depot comprising physiologically acceptable excipients and at least one delayed release active compound which is a chemotherapeutic of the gyrase inhibitor type (*see* Abstract). The depot can be used for combating infections. Wahlig et al. also teaches that tricalcium phosphate and hydroxyapatite can be used as an excipitent in the disclosed implantable medicament depot (*see* col 1, lines 15–20 and line 30). It is well known that an excipient is an inert substance used as a diluent or vehicle for a drug. (*see, e.g.*, dictionary.com). Wahlig et al. further teaches at col 4, lines 62–67 that medicament depots based on tricalcium phosphate can be made by compressing pulverulent tricalcium phosphate with the disclosed chemotherapeutic either directly or with the addition with about 1–20% of a physiologically acceptable ***binder*** which can be a collagen degradation product.

Since Wahilg et al. teaches that tricalcium phosphate and hydroxyapatite are used as only as excipitents, that is, as vehicles upon which the active chemotherapeutic compounds are delivered, there is no teaching or suggestion that tricalcium phosphate and/or hydroxyapatite have any physiological action in the disclosed medicament depots such as the restoration of

bones and dental enamel. Therefore, there is no motivation to combine the teachings of Wahlig et al. with those of Rudin et al.

The teachings of Flautre et al. do not add anything to the teachings of Wahlig et al. that would guide the skilled artisan to arrive at Applicants' claims as amended. In the last sentence of the Introduction, Flautre et al. teaches that collagen (a protein) is coated onto hydroxyapatite, which is exactly the opposite of the instantly claimed composite in which hydroxyapatite particles are associated ***onto*** a protein component. The composites taught by Flautre et al. are collagen-coated hydroxyapatite microspheres that are injectable into bones as a result of the collagen coating of the hydroxyapatite (*see* the last sentence of the first paragraph on page 63 and the first sentence of the DISCUSSION on page 65).

Furthermore, Flautre et al. discourages the use of collagen in bone formation except when it is used as a coating for hydroxyapatite and even then the collagen-coated hydroxyapatite biomaterials are disclosed as being insufficient for new bone formation (*see* CONCLUSIONS on page 67).

The combination of the teachings of Rudin et al., Wahlig et al. and Flautre et al. would not lead the skilled artisan to the instantly claimed composition because the teachings of Flautre et al. would teach away from combining the hydoxyapatite particles of Rudin et al. with a protein which functions only as a binder, as taught by Wahlig et al. For the reasons set forth above, the teachings of Flautre et al. offer no reasonable expectation that a protein-hydroxyapatite composite would successfully promote bone formation.

Claims 16–21, 28 and 31–32 were also rejected under 36 U.S.C. §103(a) as being unpatentable over PCT/1B97/01 634 to Rudin et al., in view of Wang et al., Journal of Materials Science Letters, 14, 490-492 (1995) ("Wang et al."). The Examiner contends that since Wang et al. teaches that the nanometer size hydroxyapatite deposits in an orderly way on a collagen matrix, and that Rudin et al. teaches all three dimensions of the nanoparticulate hydroxyapatite, it would be obvious to combine their teachings.

Applicants overcome this rejection by amending claim 16 to recite that the claimed composite is a microscopically heterogeneous aggregate of the nanoparticles associated onto the skeleton of the protein component. In addition, the Declaration of Tilo Poth (attached hereto as EXHIBIT A) clearly shows the effectiveness of the claimed heterogeneously structured composite, which yields superior results in the biomineralization of teeth when compared to a homogeneous composite such as that taught by Wang et al. The Declaration further supports

the claim on page 6 of the instant specification that the claimed structured composite materials according to the invention, in contrast to the prior art, lead to a particularly effective biomineralization process. The results in the Declaration further support the stated assumption in the instant specification that the particularly effective biomineralization is associated with the microstructure of the composite material and, more particularly, with the size and morphology of the calcium salt crystals, and that the longitudinal axis of the calcium salt nanoparticles represents a preferential direction for further crystal growth during the biomineralization process.

B. Double Patenting

Applicants note that the Examiner has maintained the provisional Double Patenting rejection.

IV. Conclusion

In view of the amendments and remarks above, Applicants ask for reconsideration and allowance of all pending claims. The Examiner is requested to telephone the undersigned attorney if any matter that can be expected to be resolved in a telephone interview is believed to impede the allowance of pending claims 16–21, 28 and 31–32 of United States Patent Application Serial No. 10/030,268.

Respectfully submitted,

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